Section: Ophthalmology

Research

SHORT TERM STUDY OF VISUAL AND OCT OUTCOMES OF INTRAVITREAL RANIBIZUMAB IN THE TREATMENT OF DIABETIC MACULAR EDEMA AND ITS SUBTYPES

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Abstract

Background: Diabetic Retinopathy (DR) is one of the leading causes of vision loss in adult between 20- 74 years of age . From 1990-2010, DR was ranked 5th most common cause of preventable blindness and moderate to severe visual impairment. Assessing the visual and anatomical outcome of treatment in Indian setting during a short period of 90 days and additionally, to assess the outcomes in different types of DME (OCT based classification) and different areas of macula. **Materials and Methods:** Patients with Diabetic macular edema planned for intravitreal injections who presented to our tertiary care centre were recruited for our study. All patients in the study group were assessed and treated by a single retina specialist. **Result:** 31 eyes of 31 patients with DME were included in the analysis, the mean age was 61.87 ± 7.88 in the study population. Among our study population, 19 (61.29%) participants were male and remaining 12 (38.7%) were female. Our study population comprises of 17 (54.84%) right eye and remaining 14 (45.16%) were left eye. 21 (67.74%) of our study population were associated with Hypertension and remaining 10 (32.26%) had only Diabetes Mellitus. **Conclusion:** That intravitreal ranibizumab is an effective and safe therapeutic modality for diabetic macular edema which results in rapid improvement in visual acuity and reduction in macular edema.

INTRODUCTION

Over1/3rd of the estimated 285 million people worldwide with Diabetes have signs of DR in 2010. About 1/3rd of these patients with DR have vision threatening Diabetic Retinopathy, defined as severe Non-Proliferative Diabetic Retinopathy (NPDR) or Proliferative Diabetic Retinopathy (PDR) or presence of Diabetic Macular Edema (DME).[1] In type I Diabetes Mellitus (DM), most common vision threatening lesion is PDR. However, in Type II DM, DME is a major cause of visual loss.[1] Also, in Type II DM with PDR, DME is invariably present.[1]

In a south Indian study (CURES), prevalence of diabetic retinopathy was shown to be between 17-22 percent.[1] Winsconsin Epidemiology Study of Diabetes Retinopathy (WESDR) reports a prevalence of about 29 percent of DME in long standing diabetic patients.[1]

In the past, treatment options for diabetic macular edema were limited to macular laser photocoagulation, intravitreal steroid (triamcinolone and ozurdex) and pars plana vitrectomy, in addition to adequate systemic control of Diabetes and Hypertension. Laser therapy is effective only in preventing moderate or severe visual loss and there is no significant actual improvement in vision. Another major limitation of laser therapy is the time taken for the effect to take place. Adverse effects of laser therapy are attributed to the thermo necrosis of neurosensory retina, RPE-Bruch's (retinal pigment epithelium) membrane complex or choroid depending upon the intensity and number of spots used.

Ranibizumab was the first licensed VEGF inhibitor approved for the treatment of DME. It is a humanized monoclonal antibody Fab fragment (without the Fc fragment) especially designed for

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ocular use. Current International treatment recommendations recommend the use of intravitreal injection of anti VEGF agents (ranibizumab) and have now become the standard of care for DME.
However, this study is aimed at assessing the visual and anatomical outcome of treatment in Indian setting during a short period of 90 days and additionally, to assess the outcomes in different types of DME (OCT based classification) and different areas of macula.

MATERIALS AND METHODS

Patients with Diabetic macular edema planned for intravitreal injections who presented to our tertiary care centre were recruited for our study. All patients in the study group were assessed and treated by a single retina specialist. Visual acuity was measured using a conventional, self-illuminated Snellen's chart, kept at a distance of 06 meters from the patient and best corrected visual acuity was assessed after assessment of best possible visual acuity by pinhole refraction. Similar processes of assessment were employed at baseline, 01month (after 1st dose), 02-month (1 month after 2nd dose) and 03month (1 month after 3rd dose) visits of the patient. Best corrected visual acuity (BCVA) was recorded and documented in meter/ meter format and converted into logMAR format for statistical evaluation.
Clinical evaluation of the patients was done using slit lamp biomicroscopy and indirect ophthalmoscopy by the treating retinal surgeon prior to acquisition of OCT (optical coherence tomography) macula.
OCT macula was acquired, using Cirrus OCT, Zeiss Humphrey Instruments, Dublin, CA, to confirm the macular edema as well to measure central subfield thickness (CST) and assign the type of macular edema. These were done in 'Macular Cube, 512x128' mode and automated central subfield thickness as calculated by the machine (central most numeric value in the thickness analysis) was taken as the CST at all three visits. In the interest of the patient, considered overall morphology of macula, off-centre maximal macular thickness and spread of edema (focal or diffuse), aided by Macular Change Analysis (Automated and Manual modes) by the treating Retinal surgeon to take treatment decisions (observation or switching of treatment modality).
Those patients who were decided to be treated with ranibizumab were included and followed up for 3 months. The macular edema was classified as diffuse retinal thickening (DRT), cystoid subtype (CME), serous retinal detachment (SRD) and posterior hyaloid traction (PHT) and followed up for their response to intravitreal injection ranibizumab for 3 doses of intravitreal ranibizumab injections. They were also assessed for comorbidities and complications of the treatment (endophthalmitis and thromboembolic events).

OCT Bases Subtypes
Many studies till date have described four patterns of structural changes in DME based appearance of DME on OCT: diffuse retinal thickening (sponge-like retinal swelling), CME, serous retinal detachment (SRD), and traction retinal detachment (TRD) attributable to posterior hyaloidal traction (PHT).[1,2,3,4]
In our study, DME was divided into subtypes, namely,diffuse retinal thickening, cystoid, serous retinal detachment and posterior hyaloid traction based on the morphology of the edema as seen on the OCT.
Classification of subtypes of DME in our study population were 9 (29%) cases with diffuse thickening subtype, 17 (54.8%) cases with cystoid subtype and 5 (16.13%) cases with serous retinal detachment. The cystoid subtype was the most common subtype followed by diffuse thickening and serous retinal detachment subtype. The posterior hyaloid traction subtype was not included in the study.

Statistical Analysis
Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. For normally distributed quantitative parameters the mean values were compared at day 30, day 60 and day 90 values with baseline using paired sample t-test. P value < 0.05 was considered statistically significant.

RESULTS

In our study, 31 eyes of 31 patients with DME were included in the analysis, the mean age was 61.87 ± 7.88 in the study population. Among our study population, 19 (61.29%) participants were male and remaining 12 (38.7%) were female. Our study population comprises of 17 (54.84%) right eye and remaining 14 (45.16%) were left eye. Ahmed S at el5 studied 71 eyes of 62 patients while Yoshiro M at el studied 24 eyes of 20 patients. This sample size is similar to our study population.

Association with Hypertension
21 (67.74%) of our study population were associated with Hypertension and remaining 10 (32.26%) had only Diabetes Mellitus. According to Ahsana S at el5 co-prevalence of Hypertension and Diabetes Mellitus was 13.8% (study was done in north eastern states of India). This difference in prevalence can be due to the study group comprising of different population.

HbA1c
The mean HbA1c level was 7.82± 0.67 in our study population, minimum HbA1c was 6.80 and maximum HbA1c 9.30 (95% CI 7.57 to 8.06). According to the Clinical Decision Support System

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for Diabetic Retinopathy Screening (CDSS) 1 (study done in Reus, Spain), the mean HbA1c level in Diabetics associated with DR in 2016 were 7.63 ± 1.4 which is similar to our study group.

Duration of Diabetes Mellitus

In our study, the mean duration of Diabetes Mellitus 12.13 ± 4.21 years. Minimum duration of Diabetes Mellitus was 6 years and maximum duration of Diabetes Mellitus 25 years (95% CI 10.59 to 13.67).In Ahmed S at el study, the mean duration of Diabetes was 14.17 ± 5.34 years (range 4–30 years) which was in agreement with this study.

Table 1: Distribution of studied cases according to demographic data

Demographic data	Number (%)
No. of eyes studies	31
Sex	
Male	19 (61.29%)
Female	12 (38.7%)
Eye	
Right	17 (54.84%)
Left	14 (45.16%)
Age	
>51	1 (3.2%)
51-60	12 (38.7%)
61-70	14 (45.2%)
<70	4 (12.9%)

Table 2: Status of Diabetes Mellitus and associated comorbidities.

Status	Data
Duration of Diabetes Mellitus (Years)	
Minimum-Maximum	6-25
Mean ± SD	12.13 ± 4.21
Median	11
HbA1c	
Mean ± SD	7.82 ± 0.67
Median	7.70
Hypertensive	21 (67.74%)
SD- Standard deviation	

Our study had 9 diffuse retinal thickening subtypes, 17 cystoid subtypes and 5 serous retinal detachment types.

Table 3: Distribution of subtypes of DME.

Subtypes of macular edema	Number (%)
Diffuse retinal thickening	9 (29%)
Cystoid subtype	17 (55%)
Serous retinal detachment	5 (16%)
Total	31

Mean BCVA and Visual Improvement

Mean visual acuity (in logMAR) in our study group is 0.49±0.198 at baseline, 0.41±0.191 at day 30, 0.39±0.203 at day 60 and 0.37 ± 0.199 at day 90. There is also an improvement in visual acuity of mean BCVA (logMAR) by 0.077 after the 1st dose (at day 30), 0.103after the 2nd dose (at day 60) and 0.118after 3rd dose (at day 90) from the baseline values which were statistically significant (P < 0.001). There is an improvement in visual acuity of 15.7%, 21.0% and 24.0% at day 30, 60 and 90 respectively, as compared to baseline visual acuity. Our results are in line with Ahmed S at el (which reported 19.31% improvement at 30 day of 1st dose of ranibizumab) and Seo K. H. at el (mean BCVA in logMAR was 0.50 at baseline and 0.29 at 90 day).

Table 4: Distribution of studied eyes according to LogMAR best corrected visual acuity (BCVA).

Visual acuity	Pre-injection (Day 0)	1 month after 1st injection (Day 30)	1 month after 2nd injection (Day 60)	1 month after 3rd injection (Day 90)
BCVA				
Mean±SD	0.495±0.198	0.418±0.191	0.393±0.203	0.377±0.199
Minimum- Maximum	0.18-1.00	0.18-0.78	0-0.78	0-0.78
Median	0.48	0.30	0.30	0.30
Mean improvement in visual acuity		0.077	0.103	0.118
% of improvement		15.7%	21%	24%
P value		<0.001	<0.001	<0.001
BCVA- best corrected visual acuity				

Diffuse retinal thickening:

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Mean visual acuity in diffuse retinal thickening subtype in our study group is 0.29±0.05 at baseline, 0.25±0.06 at day 30, 0.21±0.08 at day 60 and 0.20±0.07 at day 90.The improvement in BCVA (in log MAR) in this subtype of DME compared with the baseline at day 30 is 0.04 (13%), at day 60 is 0.08(27%) and at day 90 is 0.09 (31%). The improvement in visual acuity during the follow up period was statistically not significant ($P \geq 0.05$).

According to Ahmed S at el,[5] there is an improvement of 0.1 logMAR value in 30 days of 1st dose of ranibizumab. This can be due the difference in visual acuity of our study population at base line, different population and associated DME changes like hard exudates, haemorrhages.

Cystoid diabetic macular edema:

According to Ahmed S at el,[5] there is an improvement of vision in logMAR value of 0.17 in cystoid macular edema subgroup at 30 day of 1st dose of ranibizumab.

Finding in our study group is in line with visual acuity in our study group in cystoid subtype is 0.55±0.21 at baseline, 0.44±0.19 at day 30, 0.42±0.20 at day 60 and 0.42±0.19 at day 90. There is an improvement in BCVA (in logMAR) compared from the baseline with day 30, day 60 and day 90 were 0.11 (20%), 0.13(23.6%) and 0.13 (23.6%) respectively. The improvement in visual acuity during the follow up period was statistically significant ($P<0.05$) in our study.

Serous Retinal Detachment

In our study population, mean visual acuity in SRD subtypes is 0.68±0.78 at baseline, 0.65±0.60 at day 30, 0.61±0.60 at day 60 and 0.56±0.60 at day 90.

The improvement in BCVA (in logMAR) in SRD subtype of DME compared from the baseline with day 30, day 60 and day 90 are 0.03 (4%), 0.07 (10%) and 0.12 (17%) respectively. The improvement in visual acuity during the follow up period was statistically not significant ($P \geq 0.05$).

These findings are in agreement with Ahmed S at el, in which there is an improvement of vision in logMAR value of 0.05 in serous retinal detachment subgroup at 30 day of 1st dose of ranibizumab. and also with Kaya M at. el. study which reported an improvement in visual acuity in logMAR value 0.01 with a baseline value of 0.57 and 0.56 after 1 dose of ranibizumab at 1 month duration.

At the endpoint of day 90 in our study group, diffuse thickening subtype (31%) showed greater improvement in BCVA, followed by cystoid subtype (23.6%) and least by the serous retinal detachment subgroup (17%). The lower values of LogMARin our study as comparison to the Ahmed S at el in different subgroups of macular edema can be due to the different baseline visual acuity and CST in our study group and response of the ethnicity of my study population to ranibizumab.

Central Subfield Thickness

Among the patients our study group, baseline evaluation shows the mean central subfield thickness of425.45 ± 136.48 and then, it was 325.42 ± 98.85, 294.85 ± 92.02 and 273.03 ± 73.36 among the patients at day 30, day 60 and day 90 respectively. There is a significant reduction in thickness of central subfield in the 1st month after the first dose. The reduction in the thickness of central subfield gradually decreases with the subsequent doses. The amount of reduction in central subfield thickness from baseline after 1st, 2nd and 3rd dose of injection ranibizumab is 100.03 (23.5%), 130.6 (30%) and 152.42 (35.8%), respectively. The difference in the central subfield thickness across different follow up period was statistically significant (P Value <0.001).

Ahmed S at el study reported the mean preoperative CMT as per OCT was 432.0 ± 144.0 microns (range 202.0–846.0 microns). After 1 week the mean CMT was 369.0 ± 99.33 microns (range 198.0–656.0 microns) with 11.54% improvement, and after 1 month it was 341.0 ± 88.66 microns (range 191.0–608.0 microns) with 17.96% improvement. Our findings are in agreement with the results of Ahmed S at el study.

DISCUSSION

Among our patients, mean central subfield thickness in cystoid subtype of DME at baseline, day 30, day 60 and day 90 are 444.82 ± 110.46, 317.29 ±80.56, 289.82 ±75.82 and 278.05 ±68.44 respectively. Mean reduction in CST is 127.53 (28.7%) at day 30, 155 (34.8%) at day 60 and 166.76 (37.5%) at day 90. The decrease in central subfield thickness during the follow up period were statistically significant (P <0.001).

Ahmed S at el study reported the mean CST of cystoid subtype were 447.24 ± 147.24, 367.43 ± 93.41(14.55% reduction from baseline) and 347.76 ± 90.78 (19.17% reduction from baseline) at baseline, at 1 week and at 1 month respectively.

In our study, decrease in mean central subfield thickness in serous retinal detachment (SRD) subtype of DME from the baseline to the day 30, day 60 and day 90 are 130 (22.2%), 194 (33.1%) and 249.8 (42.7%). The decrease in central subfield thickness during the follow up period were statistically significant (P <0.05). This group showed linear reduction in central subfield thickness with each dose.

Among the patients at baseline, the mean central subfield thickness in SRD subtype of DME was 585.4±134.36. It was 455.4±130.32at day 30,391.4±152.93at day 60and 335.6±94.26at day 90.The difference in the central subfield thickness across different follow up period was statistically significant (P Value <0.05) at day 30, day 60 and day 90 compared to baseline.

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According to Ahmed S at el, the serous retinal detachment type showed 510.93 ± 13.01, 446.93 ± 108.09 (11.06% reduction from baseline) and 383.86 ± 91.20 (22.96% reduction from baseline) at baseline, at 1 week and at 1 month respectively.
Our study report about the SRD subtype of DME are in agreement with the above studies.

The reduction in mean central subfield thickness in diffuse thickening subtype of DME in our study group from the baseline to the day 30, day 60 and day 90 are 31.45 (10.5%), 50.56 (16.9%) and 71.23(23.7%). The decrease in central subfield thickness during the follow up period was statistically significant ($P < 0.05$) in the 60 day and 90 day. But not statistically significant at day 30. There is a linear reduction in CST but the amount of reduction is lowest as compared to other types of macular edema.
Among our patients at baseline, the mean central subfield thickness in diffuse thickening subtype of DME was 300±43.84. It was 268.55±28.89at day 30, 249.44±19.03at day 60and 228.77±40.79at day 90 among the patients. The difference in the central subfield thickness across different follow up period was statistically significant (P Value <0.05) at day 60 and day 90 compared to baseline. However, the difference at day 30 was not statistically significant (P>0.05)
Ahmed S at el reported a decrease in CST in diffuse retinal thickening subtype as306.8 ± 34.88, 296.23 ± 34.21 (3.11% reduction from baseline)and 279.31 ± 27.64(8.52% reduction from baseline) at baseline, at 1 week and at 1 month respectively.
Findings of our study are found to be lower than the findings in the above studies. This difference in finding may be due to difference in the thickness of CST of our study group at baseline as compared to the above studies and also the difference in ethnicity of the study groups between our study group and these studies may be one of the causes.
Lastly, the study showed highest reduction in mean central subfield thickness in serous retinal detachment subgroup followed by cystoid subtype and least by the diffuse retinal thickening subtype. The posterior hyaloid traction subtype was not included in our study group.

CONCLUSION

It can therefore be concluded that intravitreal ranibizumab is an effective and safe therapeutic modality for diabetic macular edema which results in rapid improvement in visual acuity and reduction in macular edema.

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